REMARKS

These remarks are in Response to the Office Communication mailed July 25, 2005. By this Response the status identifier for canceled claim 30 has been provided. Applicants maintain the right to pursue cancelled claim 30 in any related application claiming the benefit of priority of the subject Application. New claims 41 and 42, directed to the elected invention, have been added. Accordingly, upon entry of the Response, claims 1 to 4, 6 to 8, 10, 12 to 21, 23 to 25 and 28 to 42 are under consideration.

Regarding the New Claims

New claims 41 and 42 are supported throughout the specification. In particular, new claims 41 and 42 are supported, for example, by claims 1, 2 and 9, at page 8, last paragraph, through page 9, first paragraph; page 9, last paragraph, and page 11, lines 1-7. Thus, as the new claims are supported by the specification, no new matter has been added and entry thereof is respectfully requested.

I. CLAIM OBJECTIONS

The Examiner indicates that claim 30 is pending. Claim 30 was cancelled in the RCE filed January 31, 2005. By this Response, the correct status identifier for claim 30, "cancelled" is provided. Accordingly, the grounds for objection are moot. Accordingly, Applicants respectfully request that the objection be withdrawn.

II. REJECTION UNDER 35 U.S.C. §112, SECOND PARAGRAPH

The rejection of claims 1, 2, 4, 10, 24 and 28 under 35 U.S.C. §112, second paragraph, as allegedly indefinite is respectfully traversed. The grounds for rejection are due to the alleged omission of essential steps, namely, "steps for completing gene therapy." [see Office Communication, page 4]

Claims 1, 2, 4, 10, 24 and 28 are clear and definite under 35 U.S.C. §112, second paragraph. In this regard, claim 1 is directed to preventing formation of inhibitory antibodies to a blood coagulation protein delivered to a mammal by way of gene therapy, wherein said mammal has a genetic defect which can result in generation of inhibitory antibodies to a blood

coagulation protein, said method comprising administering to said mammal cyclophosphamide or anti-CD40 ligand prior to or simultaneously with said gene therapy before formation of said inhibitory antibodies. Thus, the methods can be performed on a mammal **prior to** delivery of a protein by gene therapy. Consequently, because claim 1 can be practiced prior to delivery of a protein by gene therapy, claim 1 does not omit an essential step. Accordingly, claims 1, 2, 4, 10, 24 and 28 are clear and definite under 35 U.S.C. §112, second paragraph, and Applicants respectfully request that the rejection be withdrawn.

III. REJECTIONS UNDER 35 U.S.C. §103(a)

Wilson et al., Bach and Tripathy et al.

The rejection of claims 1 to 4, 6, 10, 12 to 16, 19, 20, 28 to 33, 35, 37, 38 and 40 under 35 U.S.C. §103(a) as allegedly unpatentable over Wilson *et al.* (U.S. Patent No. 6,251,957) in further view of Bach (WO 96/25177) and Tripathy *et al.* (Nat. Med. 2:545 (1996)) is respectfully traversed. The grounds for rejection are in the record and in the Office Action mailed June 25, 2005.

Claim 30 has been cancelled without prejudice. Accordingly, the rejection of claim 30 is moot.

In order for a rejection to be proper under 35 U.S.C. §103, *inter alia*, there must be 1) a suggestion or motivation to modify or combine the references at the time of the invention; 2) the combination of references must teach or suggest each and every element of the claimed invention; and 3) a reasonable expectation of success at the time of the invention. Both the teaching or suggestion to make the claimed combination *and* the reasonable expectation of success *must both be found in the prior art, not in Applicants' disclosure.* See, e.g., *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991) and *In re O'Farrell*, 853 F.2d 894, 903-904 (Fed. Cir. 1988), *Emphasis added.* "The mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art *suggested the desirability of the modification.*" *In re Gordon,* 733 F.2d 900, 902 (Fed. Cir. 1984); *See, also, In re Mills*, 916 F.2d 680 (Fed. Cir. 1990), *Emphasis added.* Furthermore, the prior art must be considered in its entirety....including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540 (Fed. Cir. 1983).

Here, *inter alia*, there would not have been a motivation to combine or modify the cited references in order to produce the claimed methods, nor a reasonable expectation of success of producing the claimed methods, in view of Wilson *et al.*, Bach and Tripathy *et al.* alone, or in any combination, at the time of the invention. Moreover, Tripathy *et al.* and Herzog *et al.* (Blood 90, part 1, Supp. 1, abstract 1057 (1997)) each teach away from producing the claimed methods.

The claimed methods are directed to preventing or reducing formation of an inhibitory antibody to a blood coagulation protein or a protein delivered to a mammal or human by way of gene therapy. The claims require that the mammal or human have a genetic defect which can result in generation of inhibitory antibodies to a protein, or a blood coagulation protein. Claims 1 to 4, 6 to 8, 10 and 20 require, *inter alia*, that cyclophosphamide or anti-CD40 ligand, be administered prior to or simultaneously with the gene therapy before formation of said inhibitory antibodies. The claims also require, *inter alia*, delivery of a blood coagulation protein which is the "same species" as the mammal to which it is delivered. Claims 12 to 21, 23 to 25, 29 and 31 to 40 require administering an immunosuppressive agent prior to or simultaneously with gene therapy before formation of inhibitory antibodies, the delivered protein being the same species as the mammal (or human protein delivered to a human, claim 14).

As previously pointed out, Wilson *et al.* report infecting mice with recombinant adenovirus expressing human placental ALP gene, and administering either antibody to CD4+ cells, IL-12 or gamma interferon with this recombinant adenovirus. Mice treated with antibody to CD4+ cells, IL-12 or gamma interferon exhibited higher levels of human ALP expression than controls. Wilson *et al.* also report infecting mice with a recombinant adenovirus expressing human LDL receptor gene. In contrast to the claimed methods, the genes introduced into mice were human, not murine.

Furthermore, Wilson *et al.* expressly state that the method is to reduce immune response against a viral gene therapy vector (see, for example, abstract; column 2, lines 36-44; column 4, lines 35-39; and column 6, lines 16-19). Nowhere do Wilson *et al.* teach or suggest administering an immunosuppressive agent prior to or simultaneously with gene therapy before generation of inhibitory antibodies against a protein delivered to a mammal or human by way of the gene therapy, where the protein is the same species as the mammal to which it is delivered,

let alone a blood coagulation protein that is the same species as the mammal to which it is delivered. Consequently, Wilson *et al.* fail to teach or suggest and fail to motivate the skilled artisan to produce the claimed methods.

Bach (WO 96/25177, U.S. counterpart Patent Publication No. 2003/0004091) report delivering an adenovirus expressing bacterial gene along with an immunoprotective gene into mice. Bach is identical to Wilson *et al.* because the gene delivered (bacteria) is a different species than the animal to which it is delivered (mouse). Nowhere does Bach teach or suggest delivering a protein by way of gene therapy where the protein is the same species as the mammal to which it is delivered, let alone a blood coagulation protein that is the same species as the mammal to which it is delivered. Furthermore, nowhere does Bach teach or suggest administering an immunosuppressive agent prior to or simultaneously with gene therapy before generation of inhibitory antibodies against a protein delivered to a mammal or human by way of the gene therapy, where the protein is the same species as the mammal to which it is delivered, let alone a blood coagulation protein that is the same species as the mammal to which it is delivered. Thus, Wilson *et al.* and Bach alone, or in combination, fail to teach or suggest or motivate the skilled artisan to produce the claimed methods.

Moreover, because neither Wilson *et al.* nor Bach alone, or in combination, teach or suggest that an immune response is produced against a protein that is the same species as the mammal to which it is delivered, it cannot objectively be argued that Wilson *et al.* or Bach alone, or in combination, would have motivated the skilled artisan to administer an immunosuppressive agent prior to or simultaneously with gene therapy, before generation of inhibitory antibodies, when the protein delivered by way of gene therapy is the same species as the mammal, at the time of the invention. Absent such a teaching or suggestion at the time of the invention, the skilled artisan would not have had a motivation to administer an immunosuppressive agent prior to or simultaneously with gene therapy to deliver a blood coagulation protein or a protein, which is the same species as the mammal, prior to the mammal forming inhibitory antibodies against the blood coagulation protein or protein.

Neither Wilson *et al.* nor Bach even mention animals having a genetic defect which can result in generation of inhibitory antibodies to a protein, or a blood coagulation protein can be employed, let alone teach or suggest animals having such genetic defects in gene therapy

protocols. In view of the foregoing deficiencies, the skilled artisan would not have had any reason to combine Wilson *et al.* with Bach.

Tripathy *et al.* report studies of replication defective adenovirus gene therapy in mice in order to ascertain whether host immune responses were directed against viral proteins or against the transgene (see, for example, abstract and page 548). Tripathy *et al.* report that mice injected with adenovirus harboring human EPO developed anti-EPO antibodies whereas mice injected with adenovirus harboring murine EPO did not develop anti-EPO antibodies. Tripathy *et al.* fail to teach or suggest that an immune response is produced against a protein delivered by way of gene therapy when the protein is the same species as the mammal to which it is delivered. In fact, Tripathy *et al.* teach that an immune response is **not** produced against a protein delivered by way of gene therapy when the protein is the same species as the mammal to which it is delivered. Consequently, it cannot be objectively argued that Tripathy *et al.* teach or suggest administering an immunosuppressive agent prior to or simultaneously with gene therapy to deliver a protein that is the same species as the mammal prior to the mammal forming inhibitory antibodies against the protein.

As to the statement at page 7 of the Office Action, namely that "Tripathy teaches that novel proteins delivered by way of gene therapy, including deficient human proteins in patients with recessive diseases generate immune responses," the verbatim statement by Tripathy *et al.* is that "the use of RDAd encoding *non-self proteins*, including deficient human proteins in patients with recessive diseases, may generate immune responses that preclude future gene or protein therapy." (page 549, first column, *Emphasis added*) This statement is therefore clearly limited to non-self proteins, and not self proteins. In further support of Applicants position, mice injected with adenovirus harboring murine EPO did not develop anti-EPO antibodies. Tripathy *et al.* also state that "it should be noted that we did detect anti-adenovirus antibodies in both AdmEpo- and AdhEpo-injected animals. Although such antibodies did not interfere with long-term gene expression, our preliminary experiments suggest that they do preclude repeated administration of these vectors." (see, page 549, second column) Because of the presence of antibodies against human EPO and adenovirus proteins Tripathy *et al.* conclude that "it will likely be necessary to develop transient immunosuppressive regimens for the treatment of human diseases that require the repeated administration of RDAd encoding either self or foreign transgene products...." (see,

page 549, second column). Consequently, at most Tripathy *et al.* propose immunosuppressive regimens because of the generation of antibodies against adenovirus proteins or proteins of different species, not because of antibody formation against self-proteins.

As to the statement at page 7, third paragraph, of the Office Action, namely that "the art of record teaches that exposure of a novel human protein by way of gene therapy to a human deficient for the protein results in an immune response against the protein," none of Wilson *et al.*, Bach, or Tripathy *et al.* alone, or in any combination, teach or suggest that "exposure of a novel human protein by way of gene therapy to a human deficient for the protein results in an immune response against the protein." If the Examiner disagrees, Applicants respectfully request that the Examiner specifically point out where such a teaching can be found in Wilson *et al.*, Bach, or Tripathy *et al.*

As to the statement at page 7, third paragraph, of the Office Action, namely that "the method taught by Wilson taken by Bach in further view of Tripathy has the same limitations as required by the claimed method," this statement clearly evidences an improper application of 35 U.S.C. §103. As set forth above, the Federal Circuit has stated "The mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art *suggested the desirability of the modification.*" *In re Gordon,* 733 F.2d 900, 902 (Fed. Cir. 1984); *See, also, In re Mills*, 916 F.2d 680 (Fed. Cir. 1990), *Emphasis added.* Here, a motivation to combine the references is clearly lacking because, among other things, Wilson *et al.*, Bach, or Tripathy *et al.* fail to teach or suggest that "exposure of a novel human protein by way of gene therapy to a human deficient for the protein results in an immune response against the protein." Absent such a teaching or suggestion, the skilled artisan would not have had any desire to combine Wilson *et al.*, Bach and Tripathy *et al.* at the time of the invention in order to produce the claimed methods. As such, the rejection under 35 U.S.C. §103 is improper for these grounds alone and must be withdrawn.

As to the statements at page 8 of the Office Action with respect to Herzog (Blood 90:1057 (1997)), Applicants fail to understand the relevance of IM injection of AAV not activating destructive T cells response to the rejection under 35 U.S.C. §103(a). Furthermore, B cells produce inhibitory antibodies, not T cells. Thus, even if T cell responses are not activated when an AAV vector is IM injected, B cells may still produce inhibitory antibodies. Again, as

set forth in the record, Herzog Blood reports that antibodies against Factor IX following injection with an AAV vector with canine Factor IX into a hemophiliac dog (hemophilia B) were not detected. In view of the foregoing, Herzog (Blood 90:1057 (1997)) supports Applicants position that the skilled artisan would not have been motivated at the time of the invention to administer an immunosuppressive agent to prevent formation of inhibitory antibodies against a protein delivered by way of gene therapy, where the delivered protein the same species as the mammal, because antibodies against the protein were reported to be absent.

As to the statements at page 9, first paragraph, of the Office Action, Applicants fail to understand the concern with "the limitation does not require the mammal to produce inhibitory antibodies." In this regard, not all mammals form inhibitory antibodies against a protein delivered by way of gene therapy, where the delivered protein is the same species as the mammal (see, for example, Herzog, as discussed above, and Exhibits A to D, submitted herewith). Furthermore, the claimed methods are directed to "preventing or inhibiting" formation of inhibitory antibodies, and include administering cyclophosphamide or anti-CD40 ligand prior to or simultaneously with said gene therapy before formation of said inhibitory antibodies. Accordingly, a requirement that the claims recite that the mammal produce inhibitory antibodies would appear to be in conflict with the objective of the claimed methods.

As to the statements at page 9, last paragraph, of the Office Action, namely that "the mice used in the Tripathy study did not have a genetic defect which can result in generation of inhibitory antibodies," not all mammals with genetic defects produce inhibitory antibodies against the protein when delivered to the mammal. For example, as discussed in the record, Herzog (Blood 90:1057 (1997)) reported that a hemophilia B dog did not produce detectable amounts of inhibitory antibodies against Factor IX when the dog was delivered Factor IX by way of gene therapy. At least one of the dogs in these studies did not produce engogenous FIX due to a missense mutation in FIX. Furthermore, submitted herewith as Exhibits A to D are four peer review publications in which human or canine subjects with hemophilia A or hemophilia B, including subjects incapable of producing endogenous Factor IX or Factor VIII, did not produce detectable inhibitors against Factor IX (Exhibits A and B, Manno et al., Blood 101:2963 (2003), and Mount et al. Blood 99:2670 (2002), respectively) or Factor VIII (Exhibits C and D, Roth et al., N. Engl. J. Med. 344:1735 (2001), and Powell et al., Blood 102:2038 (2003), respectively).

Consequently, generation of inhibitory antibodies against a protein delivered by way of gene therapy does not always occur.

As with Wilson *et al.* and Bach, Tripathy *et al.* fail to mention using mammals having a genetic defect which can result in generation of inhibitory antibodies to a protein, or a blood coagulation protein, let alone teach or suggest using mammals having such genetic defects in gene therapy protocols. Absent such a teaching or suggestion, even if Wilson *et al.*, Bach and Tripathy *et al.* were combined, the combination fails to teach or suggest each and every element of the claimed methods.

Given the fact that none of Wilson *et al.*, Bach and Tripathy *et al.* alone, or in combination, teach or suggest that inhibitory antibodies are produced against proteins delivered by way of gene therapy to mammals, where the protein is the same species as the mammal to which it is delivered, the skilled artisan would not have been motivated to administer an immunosuppressive agent to prevent formation of inhibitory antibodies against the protein. Thus, it cannot be objectively be argued that the skilled artisan would have been motivated to administer an immunosuppressive agent to prevent formation of inhibitory antibodies against a protein delivered by way of gene therapy, where the delivered protein the same species as the mammal, when antibodies against the protein are not even formed in the absence of immunosuppressive agent.

Finally, both Herzog and Tripathy *et al.* independently report that delivery of a protein to a mammal that is the same species as the mammal, including a hemophiliac dog, did not produce detectable amounts of inhibitory antibodies against the protein. In view of the fact that both Tripathy *et al.* and Herzog report that delivery of a same-species protein did not result in production of inhibitory antibodies against the protein in any of the mammals studied, the skilled artisan would not have been motivated to administer an immunosuppressive agent prior to or simultaneously with gene therapy, when the gene encodes a protein that is the same species as the mammal to which it is delivered. Consequently, both Herzog and Tripathy *et al.* teach away from the claimed methods.

In sum, Wilson *et al.*, Bach and Tripathy *et al.* alone, or in any combination, fail to teach or suggest administering an immunosuppressive agent 1) prior to or simultaneously with gene therapy, prior to the mammal forming inhibitory antibodies against the delivered protein, where

the protein delivered by way of gene therapy is the same species as the mammal; or 2) to a mammal or human having a genetic defect which can result in generation of inhibitory antibodies to a protein, or a blood coagulation protein. Furthermore, because none of Wilson *et al.*, Bach or Tripathy *et al.* teach or suggest that inhibitory antibodies are produced against same-species proteins delivered by way of gene therapy to mammals, the skilled artisan would not have been motivated to administer an immunosuppressive agent to prevent formation of inhibitory antibodies against a same species protein. Finally, given the fact that both Tripathy *et al.* and Herzog report that no inhibitory antibodies were produced against proteins delivered to different mammals by way of gene therapy, when the proteins are the same species as the mammal to which it is delivered, Tripathy *et al.* and Herzog *et al.* both teach away from producing the claimed methods.

With respect to new claims 41 and 42, in addition to the foregoing deficiencies, none of Wilson *et al.*, Bach and Tripathy *et al.* teach or suggest anti-CD40 ligand. Absent such a teaching or suggestion, even if Wilson *et al.*, Bach and Tripathy *et al.* were combined, the combination fails to teach or suggest claims 41 or 42.

In view of the foregoing remarks and the remarks of record, claims 1 to 4, 6, 10, 12 to 16, 19, 20, 28, 29, 31 to 33, 35, 37, 38 and 40 to 42, would not have been obvious in view of Wilson *et al.*, Bach and Tripathy *et al.* alone, or in combination at the time of the invention. Consequently, the rejection under 35 U.S.C. §103(a) over Wilson *et al.* (U.S. Patent No. 6,251,957) in view of Bach (WO 96/25177) and Tripathy *et al.* (Nat. Med. 2:545 (1996)) is improper and must be withdrawn.

Wilson et al., Bach, Tripathy et al., Nilsson et al. and Warrier et al.

The rejection of claims 1, 12 to 14, 21, 23 to 25 and 39 under 35 U.S.C. §103(a) as allegedly unpatentable over Wilson *et al.* (U.S. Patent No. 6,251,957) with Bach (WO 96/25177) and Tripathy *et al.* (Nat. Med. 2:545 (1996)) in further view of Nilsson *et al.* (Proc. Natl. Acad. Sci. USA 83:9169 (1986)) and Warrier *et al.* (Blood Coag. Fibrinol. 9(Suppl 1):S125 (1998)) is respectfully traversed. The grounds for rejection are as in the record and in the Office Action mailed June 25, 2005.

The deficiencies of Wilson *et al.*, Bach and Tripathy *et al.* are discussed above. In brief, neither Wilson *et al.*, Bach or Tripathy *et al.* alone, or in any combination, teach or suggest administering an immunosuppressive agent to a mammal prior to or simultaneously with gene therapy, before formation of inhibitory antibodies, where the protein delivered by way of gene therapy is the same species as the mammal. Furthermore, neither Wilson *et al.*, Bach or Tripathy *et al.* alone, or in any combination, teach or suggest administering an immunosuppressive agent to a mammal or human having a genetic defect which can result in generation of inhibitory antibodies to a protein, or a blood coagulation protein, as in the claimed methods. Moreover, none of Wilson *et al.*, Bach, or Tripathy *et al.* alone, or in any combination, report that inhibitory antibodies are produced against proteins delivered by way of gene therapy to mammals, when the delivered protein is the same species as the mammal.

Neither Nilsson *et al.* nor Warrier *et al.* provide that which is absent from Wilson *et al.*, Bach and Tripathy *et al.* For example, Nilsson *et al.* report studies in which hemophiliacs that produce factor IX antibodies were treated with high doses of IgG with cyclophosphamide and factor IX. However, Nilsson *et al.* fail to teach or suggest administering an immunosuppressive agent prior to or simultaneously with gene therapy, before formation of inhibitory antibodies, where the delivered protein is the same species as the mammal to which it is delivered, let alone teach or suggest that an immune response is produced against a protein delivered by way of gene therapy, when the protein is the same species as the mammal to which it is delivered. Furthermore, Nilsson *et al.* fail to teach or suggest treating hemophiliacs prior to formation of inhibitory antibodies, as in the claimed methods. Nilsson *et al.* report treating hemophiliacs after they had developed inhibitory antibodies against factor IX, and is silent regarding treating hemophiliacs prior to forming inhibitory antibodies. Accordingly, Nilsson *et al.* fail to correct the deficiencies of Wilson *et al.*, Bach and Tripathy *et al.* Consequently, even if Nilsson *et al.* were combined with Wilson *et al.*, Bach, and Tripathy *et al.*, the claimed methods would not have been obvious in view of the combined references at the time of the invention.

In addition to the foregoing deficiencies, Nilsson *et al.* fail to provide 1) the requisite motivation to produce the claimed methods; 2) a reasonable expectation of success; and 3) teach away from the claimed methods. In support of Applicant's position that Nilsson *et al.* fail to provide a motivation to produce the claimed methods or a reasonable expectation of success,

Nilsson *et al.* report that in three patients, "treatment with factor IX and cyclophosphamide was ineffective, resulting in high and persistent anamnestic response." (see page 9173, first sentence under "*Discussion*") Because cyclophosphamide and factor IX treatment were reported to be ineffective, the skilled artisan would not have been motivated to produce the claimed methods, let alone have had a reasonable expectation of success at the time of the invention. Consequently, in view of Nilsson *et al.* the skilled artisan would not have been motivated nor had a reasonable expectation of success at the time of the invention of producing the claimed methods which, furthermore, would have taught away from the claimed methods.

Furthermore, Nilsson *et al.* report that cyclophosphamide combined with factor IX treatment was ineffective, which would teach the skilled artisan away from preventing or inhibiting formation of formation of inhibitory antibodies by administering cyclophosphamide, prior to or simultaneously with gene therapy, before formation of inhibitory antibodies, where the delivered protein is the same species as the mammal. With respect to the statement in reference to Applicants arguments that Nilsson *et al.* teach away from the claimed methods at page 12 of the Office Action, Applicants again respectfully remind the Patent Office must consider the art as a whole. Accordingly, the Patent Office must consider Applicants arguments that Nilsson *et al.* teach away from the claimed methods.

Moreover, the patients studied by Nilsson *et al.* had been administered factor IX protein directly. In contrast, the claimed methods are directed to preventing or inhibiting formation of inhibitory antibodies in the context of a blood coagulation protein or other protein delivered by way of gene therapy. Direct protein delivery differs from delivery of a protein by way of gene therapy. For example, inhibitory antibodies may not form when a protein is delivered by way of gene therapy whether or not inhibitory antibodies form when the same protein is directly delivered. Accordingly, in view of the fact that formation of inhibitory antibodies does not always occur in either context, the skilled artisan would not have been motivated nor had a reasonable expectation of success of producing the claimed methods in view of Nilsson *et al.* Consequently, Nilsson *et al.* cannot be said to teach or suggest the specifically claimed methods, let alone provide a motivation or reasonable expectation of success of producing the specifically claimed methods.

Warrier *et al.* report the presence of factor IX inhibitors in hemophiliacs, which is associated with the total absence of factor IX antigen due to FIX deletions or other major rearrangements; however, as with the four other cited references, Warrier *et al.* fail to teach or suggest administering an immunosuppressive agent prior to or simultaneously with gene therapy, before formation of inhibitory antibodies, where the protein delivered is the same species as the mammal to which it is delivered, let alone teach or suggest that an immune response is elicited to a protein delivered by way of gene therapy, when the protein is the same species as the mammal to which is delivered. Furthermore, as with Nilsson *et al.*, Warrier *et al.* also fail to teach or suggest treating mammals prior to formation of inhibitory antibodies. Accordingly, Warrier *et al.* fail to correct the deficiencies of Wilson *et al.*, Bach, Tripathy *et al.* and Nilsson *et al.* Consequently, even if Warrier *et al.* were combined with Wilson *et al.*, Bach, Tripathy *et al.* and Nilsson *et al.*, the claimed methods would not have been obvious in view of the combined references at the time of the invention.

At most, Warrier *et al.* suggest molecular diagnosis to identify children at greatest risk of severe hemophilia B, recommending that those with frameshift or deletion mutations be "monitored more closely during their first exposure to FIX." (page S127, right column, second full paragraph). However, Warrier *et al.* fail to even mention administering an immunosuppressive agent prior to or simultaneously with gene therapy, before formation of inhibitory antibodies, where the delivered protein is the same species as the mammal to which it is delivered, to children so diagnosed. Absent such a teaching or suggestion, Warrier *et al.* fail to provide that which is missing from Wilson *et al.*, Bach, Tripathy *et al.* and Nilsson *et al.*

In addition, the fact that Warrier *et al.* provide several possible explanations for the development of inhibitors evidences that the authors do not understand why inhibitors form. For example, one hypothesis, which the authors state "is an attractive one to consider," is that there is a deletion of neighboring genes that modulate the immune response (page S126, left column, third full paragraph). Other possible explanations include extravascular dissemination of FIX, or exposure of hemophilia patients to large amounts of exogenous protein (page S126, left column, first and second full paragraphs). Warrier *et al.* conclude by stating that "[f]urther studies are necessary to determine the precise factors responsible for these recently recognized, potentially life threatening complications of treatment in patients with haemophilia B." (page S126, right

column, first full paragraph) In view of the foregoing, Warrier *et al.* clearly fail to understand what causes inhibitory antibodies to form. Consequently, Warrier *et al.* cannot objectively be said to teach or suggest to the skilled artisan mammals having a genetic defect which can result in formation of inhibitory antibodies that may treated according to the claimed methods.

Furthermore, as in Nilsson *et al.* the patients in Warrier *et al.* had been administered factor IX protein directly. In contrast, the claimed methods are directed to preventing or inhibiting formation of inhibitory antibodies in the context of a blood coagulation protein or other protein delivered by way of gene therapy, and as discussed above, inhibitory antibodies may not form when a protein is delivered by way of gene therapy whether or not inhibitory antibodies form when the same protein is directly delivered. Accordingly, in view of the variability of inhibitor antibody formation, the skilled artisan would not have been motivated nor had a reasonable expectation of success of producing the claimed methods in view of Warrier *et al.* Consequently, Warrier *et al.* cannot be said to teach or suggest the specifically claimed methods, let alone provide a motivation or reasonable expectation of success of producing the specifically claimed methods.

Moreover, as discussed above and in the record, Tripathy *et al.* and Herzog *et al.* each report that mammals delivered same-species proteins via gene therapy did not produce inhibitory antibodies against the delivered proteins and, therefore, the skilled artisan at the time of the invention would have had no logical reason to use an immunosuppressive agent prior to or simultaneously with gene therapy, when the gene encodes a protein that is the same species as the mammal to which it is delivered. The reports of Tripathy *et al.* and Herzog *et al*, namely that mammals (humans and dogs) delivered same-species proteins do not produce inhibitory antibodies against the proteins are corroborated by Exhibits A to D submitted herewith. Again, because no immune response was elicited against the same-species protein delivered by way of gene therapy there is no logical reason to administer an immunosuppressive agent prior to or simultaneously with gene therapy. Consequently, each of Tripathy *et al.* and Herzog *et al.*, as corroborated by Exhibits A to D, teach the skilled artisan away from producing claims 1, 12 to 14, 21, 23 to 25 and 39.

With respect to new claims 41 and 42, in addition to the foregoing deficiencies, neither Nilsson *et al.* nor Warrier *et al.* teach or suggest anti-CD40 ligand. Absent such a teaching or

suggestion, even if Nilsson *et al.* nor Warrier *et al.* were combined with Wilson *et al.*, Bach and Tripathy *et al.*, the combination fails to teach or suggest claims 41 or 42.

Finally, with respect to the assertion in the Office Action at page 12, third paragraph, that "one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references," Applicants respectfully remind the Patent Office that in order for a rejection under to be proper, *there must have been a suggestion or motivation to modify or combine the cited references at the time of the invention.* Accordingly, absent a motivation to combine Wilson *et al.*, Bach, Tripathy *et al.*, Nilsson *et al.* and Warrier *et al.* at the time of the invention, a rejection under 35 U.S.C. §103(a) is improper on this basis alone and must be withdrawn. Applicants have presented arguments and provided evidence herein and in the record in support of an absence of the requisite motivation to combine Wilson *et al.*, Bach, Tripathy *et al.*, Nilsson *et al.* and Warrier *et al.* at the time of the invention. Furthermore, even if for the sake of argument there was a motivation to combine Wilson *et al.*, Bach, Tripathy *et al.*, Nilsson *et al.* and Warrier *et al.* at the time of the invention, if the combination fails to teach or suggest each and every element of the claimed methods, a rejection under 35 U.S.C. §103(a) is improper and must be withdrawn. Applicants have also presented arguments and provided evidence herein and in the record that the combination of Wilson *et al.*, Bach, Tripathy *et al.*, Nilsson *et al.* and Warrier *et al.* fail to teach or suggest each and every element of the claimed methods.

In view of the foregoing, claims 1, 12 to 14, 21, 23 to 25, 39, 41 and 42 would not have been obvious over Wilson *et al.*, Bach, Tripathy *et al.*, Nilsson *et al.* and Warrier *et al.* alone, or in any combination, at the time of the invention. Consequently, the rejection under 35 U.S.C. §103(a) over Wilson *et al.* (U.S. Patent No. 6,251,957) with Bach (WO 96/25177) and Tripathy *et al.* (Nat. Med. 2:545 (1996)) in view of Nilsson *et al.* (Proc. Natl. Acad. Sci. USA 83:9169 (1986)) and Warrier *et al.* (Blood Coag. Fibrinol. 9(Suppl 1):S125 (1998)) is improper and must be withdrawn.

Wilson et al., Bach, Tripathy et al. and Herzog et al.

The rejection of claims 1, 3, 6 to 8, 13, 14, 16 to 18, 33 to 36 and 40 under 35 U.S.C. §103(a) as allegedly unpatentable over Wilson *et al.* (U.S. Patent No. 6,251,957) with Bach (WO

96/25177) and Tripathy *et al.* (Nat. Med. 2:545 (1996)) in further view of Herzog *et al.* (Proc. Natl. Acad. Sci. USA 94:5804 (1997), referred to herein as "Herzog PNAS") is respectfully traversed. The grounds for rejection are as in the record.

Claims 1, 3, 6 to 8, 13, 14, 16 to 18, 33 to 36 and 40 would not have been obvious in view of Wilson *et al.*, Bach, Tripathy *et al.*, and Herzog PNAS alone, or in any combination. First, with respect to the assertion in the Office Action at page 13, last paragraph, that "one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references," Applicants reiterate that in order for a rejection under 35 U.S.C. §103(a) to be proper, there must have been a suggestion or motivation to modify or combine the cited references at the time of the invention. Accordingly, absent a motivation to combine Wilson *et al.*, Bach, Tripathy *et al.*, and Herzog PNAS at the time of the invention, on this basis alone a rejection under 35 U.S.C. §103(a) is improper and must be withdrawn. Applicants have presented arguments and provided evidence herein and in the record in support of an absence of the requisite motivation to modify or combine Wilson *et al.*, Bach, Tripathy *et al.* and Herzog *et al.* at the time of the invention. Furthermore, even if for the sake of argument there was a motivation to combine Wilson *et al.*, Bach, Tripathy *et al.* and Herzog *et al.* at the time of the invention, if the combination fails to teach or suggest each and every element of the claimed methods, a rejection under 35 U.S.C. §103(a) is improper and must be withdrawn. Applicants have also presented arguments and provided evidence herein and in the record that the combination of Wilson *et al.*, Bach, Tripathy *et al.* and Herzog *et al.* fail to teach or suggest each and every element of the claimed methods.

The deficiencies of Wilson *et al.*, Bach and Tripathy *et al.* have been discussed at length above and in the record. In brief, neither Wilson *et al.*, Bach nor Tripathy *et al.* alone, or in any combination, teach or suggest administering an immunosuppressive agent to a mammal prior to or simultaneously with gene therapy, before formation of inhibitory antibodies, where the protein delivered by way of gene therapy is the same species as the mammal, or administering an immunosuppressive agent to a mammal or human having a genetic defect which can result in generation of inhibitory antibodies to a protein, or a blood coagulation protein, as in the claimed methods. Furthermore, none of Wilson *et al.*, Bach, or Tripathy *et al.* alone, or in any combination, teach or suggest that inhibitory antibodies are produced against proteins delivered

by way of gene therapy to mammals, when the delivered protein is the same species as the mammal.

Herzog PNAS does not provide that which is absent from Wilson *et al.*, Bach and Tripathy *et al.* In brief, Herzog PNAS reports injection of recombinant adeno-associated virus vector expressing human factor IX in hindlimb of mice, which developed antibodies against human factor IX. Subsequent studies in which rag 1 mice were injected were reported to produce therapeutic levels of human factor IX in plasma. However, as with all other cited references, Herzog PNAS does not teach or suggest administering an immunosuppressive agent to a mammal prior to or simultaneously with gene therapy, prior to formation of inhibitory antibodies, where the protein delivered by way of gene therapy is the same species as the mammal to which it is delivered. Nor does Herzog PNAS teach or suggest that inhibitory antibodies are produced against a protein delivered by way of gene therapy, where the delivered protein is the same species as the mammal to which it is delivered. Finally, Herzog PNAS fails to teach or suggest administering an immunosuppressive agent to a mammal or human having a genetic defect which can result in generation of inhibitory antibodies to a protein, or a blood coagulation protein, let alone in the manner claimed. Absent such a teaching or suggestion, Herzog PNAS fails to provide that which is missing from Wilson *et al.*, Bach and Tripathy *et al.* and, therefore, even if combined with Wilson *et al.*, Bach and Tripathy *et al.*, fail to teach or suggest the claimed methods.

With respect to new claims 41 and 42, in addition to the foregoing deficiencies, Herzog PNAS fails to teach or suggest anti-CD40 ligand. Absent such a teaching or suggestion, even if Herzog PNAS were combined with Wilson *et al.*, Bach and Tripathy *et al.*, the combination fails to teach or suggest claims 41 or 42.

In view of the foregoing, claims 1, 3, 6 to 8, 13, 14, 16, 33 to 36, 41 and 42 would not have been obvious in view of Wilson *et al.*, Bach, Tripathy *et al.*, or Herzog PNAS alone, or in any combination, at the time of the invention. Consequently, the rejection under 35 U.S.C. §103(a) over Wilson *et al.* (U.S. Patent No. 6,251,957) with Bach (WO 96/25177) and Tripathy *et al.* (Nat. Med. 2:545 (1996)) in view of Herzog *et al.* (Proc. Natl. Acad. Sci. USA 94:5804 (1997)) is improper and must be withdrawn.

CONCLUSION

In summary, for the reasons set forth herein, Applicants maintain that claims 1 to 4, 6 to 8, 10, 12 to 21, 23 to 25 and 28 to 42 clearly and patentably define the invention, respectfully request that the Examiner reconsider the various grounds set forth in the Office Action, and respectfully request the allowance of the claims which are now pending.

If the Examiner would like to discuss any of the issues raised in the Office Action, Applicant's representative can be reached at (858) 509-4065.

Please charge any additional fees, or make any credits, to Deposit Account No. 50-2212.

Respectfully submitted,

Date: January 25, 2006

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CERTIFICATION UNDER 37 C.F.R. §§ 1.8 and/or 1.10*

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